PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ZRC-MC-007	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IN 03/00081	International filing date *(day/month/year)* 26.03.2003	Priority date *(day/month/year)* 01.04.2002
International Patent Classification (IPC) or both national classification and IPC C07D413/12		
Applicant CADILA HEALTHCARE LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.10.2003	21.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fazzi, R Telephone No. +49 89 2399-8510

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IN 03/00081

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-4, 6-64	as originally filed
5	received on 05.04.2004 with letter of 02.04.2004

Claims, Numbers

1 (part), 2 (part), 3-22	as originally filed
1 (part), 2 (part)	received on 05.04.2004 with letter of 02.04.2004

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 7-10 and 14-17

because:

☒ the said international application, or the said claims Nos. 7-10 and 14-17 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☒ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-22
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-6, 11-13, 18-22
	No:	Claims	

2. Citations and explanations

see separate sheet

1) Reference is made to the following documents:

D1: WO 02 06278 A
D2: WO 99 64417 A
D3: WO 01 58885 A
D4: WO 98 01447 A
D5: WO 93 23384 A
D6: PAE A N ET AL: '3D QSAR studies on new oxazolidinone antibacterial agents by comparative molecular field analysis' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 18, 20 September 1999 (1999-09-20), pages 2685-2690, XP004179952 ISSN: 0960-894X
D7: BRICKNER S J ET AL: 'Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections' JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, no. 3, 2 February 1996 (1996-02-02), pages 673-679, XP000574381 ISSN: 0022-2623
D8: TOKUYAMA R ET AL: 'Structure-Activity Relationship (SAR) Studies on Oxazolidinone Antibacterial Agents. 3. Synthesis and Evaluation of 5-Thiocarbamate Oxazolidinones' CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 49, no. 4, April 2001 (2001-04), pages 361-367, XP001145544 ISSN: 0009-2363
D9: BRICKNER S J: 'Oxazolidinone Antibacterial Agents' CURRENT PHARMACEUTICAL DESIGN, BENTHAM SCIENCE PUBLISHERS, SCHIPHOL, NL, vol. 2, 1996, pages 175-194, XP001007528 ISSN: 1381-6128

2) Amendments (Reference to section I.6)

The amendments filed with letter dated 02/04/2004 do not introduce any subject-matter which extends beyond the content of the application as originally filed, so as to comply with the requirements of Article 34(2b) PCT.
Said amendments concern the deletion of the substituent "O-heterocyclyloxy" from the definition of W in claim 1 and in the corresponding page 5 of the description.

3) Reference to section III

Claims 7-10 and 14-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

4) Unity of invention (Reference to section IV)

With the amendments filed with letter of 02/04/2004 the Applicant has deleted the feature "O-heterocyclyloxy" from the substituent W in claim 1, thus rendering the subject-matter of present claim 1 new over the state of the art and overcoming the non-unity objections raised in the International Search Report.
In said letter the Applicant has also underlined the technical feature linking the three different subparts of present claim 1, namely formula (I) where Y can be either G_1, G_2 or G_3. This technical feature is represented by the *piperazine ring attached to either a substituted or unsubstituted alkenyl or alkynyl group or a substituted or an unsubstituted alicyclic system containing a -C=X group in the α-position with respect to the point of attachment with the linker*. This unifying concept of the present application is also responsible for a teaching over the state of the art in terms of novelty and inventive step.

Consequently, the requirements of Rule 13 PCT are fulfilled.

5) Novelty (Reference to section V)

D1 discloses compounds of general formula (I) differring from the present ones in the definition of the groups R-T-W and R_1 (cf. claim 1 of D1).

After the amendments carried out by the Applicant in which the substituent "O-heterocyclyloxy" has been deleted from the definition of present W group, the subject-matter of current claim 1 can be considered new over D2 in that it lacks the feature -X-Het of formula (I) of D2 (cf. page 2 of D2 and the definition of current W group on amended page 5 of the description).

D3 differs from the subject-matter of present claim 1 in the definition of the group R_4 (cf. page 2 of D3 in comparison with the definition of present Y substituent).

The same considerations apply as well to documents D4-D7, which differ from the subject-

matter of present claim 1 in the definition of substituents corresponding to present Y group (cf. D4 on page 2; D5 on pages 1-2; D6 on page 2688 and D7 on page 675).

D8 and D9 represent less relevant technological background.

Thus, the subject-matter of present claims 1-22 is new in the sense of Article 33(2) PCT.

6) Inventive step (Reference to section V)

In view of the cited documents, the problem to be solved by the present application may be seen in the provision of further compounds to be useful against Gram-positive and Gram-negative pathogens.
Although all the cited documents of the state of the art relate to the same technical problem, none of them suggests a substitution such as that represented by the present Y group, which was underlined in paragraph 4 above, and which can be considered as the inventive contribution of the present application over the prior art.
For this reason, the subject-matter of present claims 1-22 is deemed to fulfil the criteria set forth in Article 33(3) PCT.
However, it is to be noticed after the entrance in the European Phase, attention will be drawn to the breadth of the main claim, which should represent a reasonable generalisation over the **tested** examples provided (namely those on page 64 of the description), and should also be supported by the description.
Attention will also be given to the Applicant's arguments sent with letter of 02/04/2004, stating that "a modification in the structure of a compound significantly changes its physico-chemical as well as biological properties" (cf. page 3 of said letter) or that "any change in the structure of the compound, **howsoever minor it may look on the face of it**, changes the compound profile and affects the efficacy, toxicity and characteristics of the drug candidates" (cf. page 13 of the same letter).

7) Industrial applicability (Reference to section V)

For the assessment of the present claims 7-10 and 14-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known com-

pound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

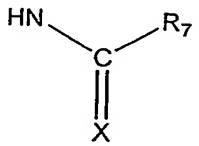
8) Further observations

8.1)A mistake has probably occurred when citing the document on page 2, lines 4-5 of the description (*J. Med. Chem.* 1992, 35, 2569-78, Gregory W. A. et al.), which could not be found.

8.2) Prodrug: protection cannot be sought for speculative compounds, which have yet to be prepared and investigated. Although there is an indication within the application as to what it may be, a prodrug is not a definable term as regards its structure. The skilled person has no indication as to what falls within this definition, and it should thus be deleted. No analysis of novelty and inventive step has therefore been made for all the compounds which are combinations of "prodrug" and of derivatives of formula (I) (cf. page 27 and claims 5, 18 and 19).

aryl, heteroaryl, heterocyclyl groups; the dotted line'------' represents either a bond or a no bond.

W represents OH, N_3, NH_2,NCS, OSO_2CH_3 O-heterocyclyloxy or a moiety of general formula



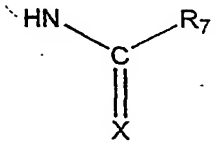
Wherein R_7 may be H, substituted or unsubstituted groups selected from amino, alkylamino, dialkylamino, aralkylamino, C_1-C_6alkoxy, C_1-C_{12}alkyl, aralkyl, C_3-C_{12}cycloalkyl, C_1-C_6thioalkyl, C_1-C_6haloalkyl, thioalkoxy, and X is selected from O, S, -NR_5 where R_5 represents H, or substituted or unsubstituted alkyl group or aryl groups.

Suitable rings representing A may be selected from but are not limited to 5-6 membered ring systems which may be single or fused and examples of ring moieties in G_1 may be cyclohexanone, cyclopentanone, α-tetralone, indanone, 6-methoxy-α-tetralone, 5-methoxy tetralone, indole, 5-methoxy indanone, dihydrobenzothiophenone and the like.

Suitable substituents on groups A & Z may be selected from cyano, nitro, halo, perhaloalkyl, carboxyl, hydrazino, azido, formyl, amino, thio, hydroxy, sulfonyl, or substituted or unsubstituted groups selected from alkyl which may be linear or branched; cycloalkyl, alkenyl, cycloalkenyl, alkynyl, hydrazinoalkyl, alkylhydrazido, hydroxylamino, acyl, acyloxy, acylamino, carboxyalkyl, haloalkyl, aminoalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, thioalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylaminoalkyl, arylamino, alkylamino, aralkylamino, aralkoxy, haloaralkyl, aralkenyl, aryl, aralkyl, aryloxy, alkoxy, alkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylcarbonylalkyl, alkoxycarbonylalkyl, 1-alkoxycarbonyloxy-alkyl, 1-cycloalkyloxycarbonyloxy-alkyl, carboxamidoalkyl, cyanoamidino, cyanoalkyl, aminocarbonylalkyl, N-aminocarbonylalkyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, carboxyalkylaminocarboxy, N-alkylamino, N,N-dialkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, N-alkylaminoalkyl, N,N-dialkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-aralkyl-N-alkylaminoalkyl, N-alkyl-N-arylaminoalkyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, N-alkyl-N-

haloalkoxy, perhaloalkoxy, substituted or unsubstituted groups selected from cycloalkyl, bicycloalkyl, (C_1-C_{12})alkoxy, cyclo(C_3-C_7)alkoxy, aryl, aryloxy, aralkyl, ar(C_1-C_{12})alkoxy, heterocyclyl, heteroaryl, heterocyclyl(C_1-C_{12})alkyl, heteroar(C_1-C_{12})alkyl, heteroaryloxy, heteroar(C_1-C_{12})alkoxy, heterocycloxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, carboxylic acid and its derivatives such as esters and amides, hydroxyalkyl, aminoalkyl, mono-substituted or di-substituted aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, (C_1-C_{12})alkylthio, thio(C_1-C_{12})alkyl, arylthio, SOR_6 and SO_2R_6, where R_6 represents amino, optionally substituted groups selected from alkyl, aryl, heteroaryl, heterocyclyl groups; the dotted line'------' represents either a bond or a no bond.

W represents OH, N_3, NH_2,NCS, OSO_2CH_3 O-heterocyclyloxy or a moiety of general formula



Wherein R_7 may be H, substituted or unsubstituted groups selected from amino, alkylamino, dialkylamino, aralkylamino, C_1-C_6alkoxy, C_1-C_{12}alkyl, aralkyl, C_3-C_{12}cycloalkyl, C_1-C_6thioalkyl, C_1-C_6haloalkyl, thioalkoxy, and X is selected from O, S, $-NR_5$ where R_5 represents H, or substituted or unsubstituted alkyl group or aryl groups.

2. A compound as defined in **claim 1** wherein substituents on groups A & Z are selected from cyano, nitro, halo, perhaloalkyl, carboxyl, hydrazino, azido, formyl, amino, thio, hydroxy, sulfonyl, or substituted or unsubstituted groups selected from alkyl which may be linear or branched; cycloalkyl, alkenyl, cycloalkenyl, alkynyl, hydrazinoalkyl, alkylhydrazido, hydroxylamino, acyl, acyloxy, acylamino, carboxyalkyl, haloalkyl, aminoalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, thioalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylaminoalkyl, arylamino, alkylamino, aralkylamino, aralkoxy, haloaralkyl, aralkenyl, aryl, aralkyl, aryloxy, alkoxy, alkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylcarbonylalkyl, alkoxycarbonylalkyl, 1-alkoxycarbonyloxy-alkyl, 1-cycloalkyloxycarbonyloxy-alkyl, carboxamidoalkyl, cyanoamidino, cyanoalkyl, aminocarbonylalkyl, N-aminocarbonylalkyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, carboxyalkylaminocarboxy, N-